In That Issue: Proceedings From the Third Intercontinental Meeting of Hair Research Societies

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FOLLICULAR BIOLOGY AS MICROCOSM OF CUTANEOUS BIOLOGY

The interests of dermatologists and skin biologists have invariably included hair as a target of investigation. Seventy years ago, Andrews devoted 20 of 1000 pages to hair abnormalities in the popular textbook "Diseases of the Skin" (Andrews, GC: Disease of the Skin, W.B. Saunders, Philadelphia, 1932). Major portions of these 20 pages were devoted to genetic abnormalities, alopecia areata, scarring alopecias, and hypertrichosis (including a large section on hair depilation). Over the ensuing 70 years, much has changed, but the diseases have not. During these 70 years, the discipline of dermatology has developed a scientific base, a base in which stem cells, mesenchymal–epithelial interaction, and molecular genetics dominate the scientific landscape. Importantly, research on hair has participated in this transition, even to the extent that hair biology may be seen as a microcosm of skin biology in general. Much of the recent progress in this field was discussed at the International Hair Workshop which took place last year in Tokyo Japan. This special issue of the *Journal of Investigative Dermatology Symposium Proceedings* serves as a record of the progress revealed in that workshop. To provoke interest, we emphasize below several of the developments that typify that progress.

BIOCHEMICAL MECHANISMS AND HAIR PHYSIOLOGY

Modulation of gene expression by steroid hormones Knowledge about the roles of steroid hormones in the development and homeostasis of skin remains in its infancy. McPhaul presented contemporary information about the factors that mediate and modulate androgen action. In mammals, although a number of steroids can be shown to exert androgenic effects using *in vitro* and *in vivo* assays, testosterone and its reduced metabolite, 5′-dihydrotestosterone are thought to represent the principal physiologic androgens. At present, a body of increasingly detailed information is available concerning the mechanisms by which nuclear receptors, such as the androgen receptor, regulate the activity of target genes. Knowledge about the regulation of genes by androgens in normal physiology and in disease states is in only its earliest stages.

Biochemistry and the development of finasteride Shapiro and Kaufman reported on the use of finasteride in treating male-pattern alopecia. This molecule was the first highly specific inhibitor of human type 2 5′-reductase developed for clinical use. Accumulated data from multicenter clinical trials have established finasteride's importance as a treatment for men with androgen-dependent alopecia. Its effectiveness has prompted the development of other inhibitors of 5′-reductase, as well as research on other modulators of androgen action in skin.

STEM CELLS

Hair follicle stem cells Headed by Lavker, the workshop on hair follicle stem cells brought together investigators who have used a variety of approaches to understand the biology of follicular epithelial stem cells and regulation of hair cycle. Follicular epithelial stem cells are multipotent, capable of giving rise not only to all the cell types of the hair, but also to the epidermis and the sebaceous gland. With respect to their location, immunohistochemical and ultrastructural data were presented indicating that cells with stem cell attributes were localized to the prominent bulge region of developing human fetal hair follicles.

Negative selection for hair follicle stem cells Matic and Simon presented data suggesting that connexin 43 (Cx43), a gap junction protein present in human epidermis and mouse hair follicles, can serve as a negative marker for keratinocyte stem cells. In mouse pelage and vibrissae hair follicles, most of the slowly cycling cells, detected as label-retaining cells, do not express Cx43. In humans, cells with undetectable levels of Cx43 are found in the epidermal basal layer of neonatal foreskin, and in the follicular bulge region. About 10% of the basal keratinocytes are Cx43 negative. These cells are uniformly small and low in granularity, suggesting that keratinocyte stem cells can be separated based on Cx43 expression.

ANIMAL MODELS AND *IN VITRO* MODELS

Epithelial–mesenchymal interactions Randall and colleagues reviewed the utility of animal models and *in vitro* models. Botchkarev and Kishimoto reviewed the importance of epithelial–mesenchymal interactions, which play pivotal roles in the morphogenesis of many organs and various types of appendages. Tobin reviewed issues concerning the plasticity of hair follicle mesenchyme during the growth cycle. Although hair follicle mesenchyme is widely believed to consist of stable cell populations, new data indicate that follicular papilla cell number increases during anagen and that this increase is driven primarily by cell proliferation in the proximal connective tissue sheath. Plasticity of the FP and CTS is likely to be a critical element, not only for hair cycle control, but also for hair follicle transformations from vellus-to-terminal and back.

ALOPECIA AREATA HAS LESSONS ABOUT AUTOIMMUNE SKIN DISEASE

McElwee and colleagues reviewed recent experiences with the experimental autoimmune rodent models currently employed to understand mechanisms of disease initiation and progression.

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Current research suggests a self-contained disease cycle that involves four immunoregulatory events: (1) Failure of the putative hair follicle immune privilege during anagen with exposure of follicular epitopes to: the immune system; (2) Presentation of epitopes, costimulation, and activation of responsive lymphocytes by antigen presenting cells; (3) Migration of activated inflammatory cells into hair follicles; and (4) A disruptive action of the inflammatory cells within hair follicles. In microcosm, this is the mechanism of virtually all autoimmune skin diseases.

Treatment of alopecia areata may be based on immune intervention. Freyschmidt-Paul and her colleagues addressed the futility of many conventional treatments for alopecia areata, proposing that possible future therapeutic approaches focus on immunomodulatory agents such as TGF-β and IL-10; inhibition of apoptosis mediated by the Fas-FasL system; inhibition of the lymphocyte homing receptor CD44v10; and induction of tolerance. Liren Tang and colleagues have already begun to test the impact of conventional therapeutic modalities on cytokines and signal transduction pathways in a rodent model of alopecia areata. To test whether immune cytokines might be modulated by anthralin, an RNase protection assay (RPA) and the real time polymerase chain reaction (PCR) were performed to compare their expression between anthralin-treated and control skins. These experiments showed that expression of proinflammatory cytokines TNF-α and IFN-γ was inhibited by anthralin, while expression of IL-1a/ and their receptor antagonist, IL-1R′, and immunosuppressive IL-1α was stimulated by anthralin. Tsuji and colleagues observed in work on the role of TGF-ß in alopecia areata that a novel plant extract would effectively suppress TGF-ß action. Their results suggest that the induction of catagen by TGF-ß is mediated via activation of caspases and that suppression of TGF-ß could be effective in preventing male pattern baldness.

Lessons from Fas-deficient and FasL-deficient mice Freyschmidt-Paul and colleagues studied alopecia areata to elucidate whether the Fas-FasL pathway is of pathogenetic significance using exchanged skin grafts. Skin-grafts from control mice developed hair loss, whereas Fas-deficient and FasL-deficient skin-grafts were spared from significant hair loss. The results suggest that the Fas/FasL pathway plays a pathogenetic role in AA.

SCARRING ALOPECIAS

Olsen and her colleagues reviewed difficulties in developing a nosology for the scarring alopecias. Based on a workshop held earlier at Duke University Medical Center, they have developed a preliminary system for classifying the entities that make up the scarring alopecias. This classification should be of considerable use to clinical investigators as they attempt to address mechanisms of the various diseases that make up the scarring alopecias.

ANDROGENETIC ALOPECIA

Price reviewed the background of androgenetic alopecia (AGA) in women. Both young women and young men with AGA have higher levels of 5α reductase and androgen receptors in frontal hair follicles compared to occipital follicles. At the same time, young women have much higher levels of cytochrome p-450 aromatase in frontal follicles than men who have minimal aromatase, and women have even higher aromatase levels in occipital follicles. Unfortunately, topical minoxidil solution is as yet the only drug available for promoting hair growth in women with AGA.

Inui and colleagues identified androgen-inducible TGF-ß1 derived from dermal papilla cells as a mediator in androgenetic alopecia. Their work suggests that androgen-inducible TGF-ß1 derived from dermal papilla cells mediates hair growth suppression in androgenetic alopecia.

MEASURING HAIRS AND HAIR GROWTH

Hoffmann emphasized the need for a sensitive tool to monitor hair loss and treatment responses. Briefly stated, such a method must be able to analyze the biological parameters of hair growth, which are: hair density, hair diameter, growth rate, anagen/telogen ratios. They have presented the TrichoScan as a method that combines epiluminescence microscopy with automatic digital image analysis to measure hair *in situ*. The TrichoScan is able to analyze all four parameters of hair growth with a so-called intraclass correlation of approximately 91% within the same TrichoScan operator and an intraclass correlation of approximately 97% for different TrichoScan operators. Advantages of the TrichoScan are that it can be used for clinical studies to compare placebo vs. treatment, to compare different capacities of hair growth promoting substances, to study AGA and other forms of diffuse hair loss, and to study the effects of drugs and laser treatment on hypertrichosis and hirsutism.

Ueki and colleagues reported on hair growth patterns of one hundred one Japanese female subjects with diffuse, chronic hair loss and 58 healthy Japanese female volunteers who were categorized into subgroups using noninvasive quantitative methods after determining the key parameters of hair growth. The Phototrichogram was performed at 0 and 48 h after clipping hairs in the parietal region of the scalp. Shaft diameters of the excised hairs were then measured. Multiple regression analysis indicated that hair densities, hair diameters, short hair ratios and hair growth rates, but not anagen hair ratios, were significant, in order of decreasing importance, for grading female diffuse alopecia. Hair patterns showing a decrease in hair density but without vellus hair change, emerged as the most prevalent and distinct pattern of chronic diffuse hair loss among the Japanese female subjects.

CHARACTERIZATION OF HUMAN KERATIN ASSOCIATED PROTEIN (hKAP) 1 FAMILY MEMBERS

Shimomura presented data about keratin-associated proteins (KAPs), which are involved in formation of the cross-linked network of the keratin-intermediate filament proteins that support hair fibers. In recent years, several KAP genes have been identified and become an attractive topic in hair research. More recently, they isolated two cDNAs encoding novel members of the human KAP1 family, hKAP1.6 and hKAP1.7, and described their expression in the hair follicle by RNA *in situ* hybridization. A comparison of hKAP1.6 and hKAP1.7 with other human KAP1 members revealed that KAP1 proteins are fundamentally composed of five distinct domains, and that they can be classified primarily by a striking variation in double cysteine-containing pentapeptide repeats in the repetitive I domain.

FATE OF MELANOCYTES DURING DEVELOPMENT OF THE HAIR FOLLICLE PIGMENTARY UNIT

During hair follicle morphogenesis, melanocyte precursors migrate into developing hair follicles and give rise to differentiated melanocytes that actively produce and transport pigment into the keratinocytes that form the hair shaft. However, patterns of melanocyte proliferation and differentiation during formation of the hair pigmentation unit remain to be elucidated. Their data suggests that melanocyte precursor cells proliferate extensively at the onset of follicle development. Progeny of these cells migrate down the developing follicle, differentiating further until reaching the area immediately above the dermal papilla, where fully differentiated nonproliferative melanin-producing melanocytes persist, contributing pigment to the growing hair shaft.